Chapter

Introductory Chapter: Oral Selinexor, a Selective Inhibitor of Nuclear Export in the Treatment of Patients with Multiple Myeloma Refractory to Proteasome Inhibitors, Immunomodulatory Agents and Monoclonal Antibodies

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1. Introduction

The export of proteins from the nucleus to the cytoplasm plays an important role in the development of cancer and drug resistance [1–3]. The major mammalian nuclear export receptor protein is exportin 1 (XPO1, also known as chromosomal maintenance 1/ CRM1/) [1–5]. The crystal structure of this protein showed a complex with the Ran protein (Ras-related nuclear protein) bound to GTP [6, 7]. XPO1 interacts also with nucleoporins in the nuclear pore complex and transports multiple tumor suppressor proteins (eg p53, FOXO, p21 pRB, BRCA1/2), growth regulators, and oncoprotein mRNAs (eg c-myc, Bcl-xL, MDM2, cyclins) containing a leucine rich nuclear export signal (NES) (**Figure 1**) [8]. XPO1 is also involved in regulation of cytoplasmic localization and translation of c-myc and other oncoprotein mRNAs (eg cyclin D1, Bcl-6, Mdm2, and Pim) through complexing with eukaryotic initiation factor 4E (eIF4E) [9]. The XPO1 protein level is increased in many types of cancer including multiple myeloma [10–13]. As a result of the increased nuclear-cytoplasmic transport in cancer cells, an elevated level of multiple tumor suppressor proteins and oncoproteins in the cytoplasm leads to advanced disease, resistance to therapy, and poor survival. Thus, XPO1 is a promising cancer drug target. Leptomycin B (LMB) is a Streptomyces metabolite that inhibits the function of XPO1 in NES-dependent nuclear export of proteins [14]. However, clinical studies found serious side effects of LMB. In order to find a more specific inhibitor of XPO1 without side effects, many natural and synthetic compounds have been tested. These compounds include selinexor (KPT-330, XPOVIO™), verdinexor (KPT-335), KPT-185, KPT-276, KPT-251, and KPT-8602 [15–18]. These agents are a family of small molecules that block nuclear export through covalent

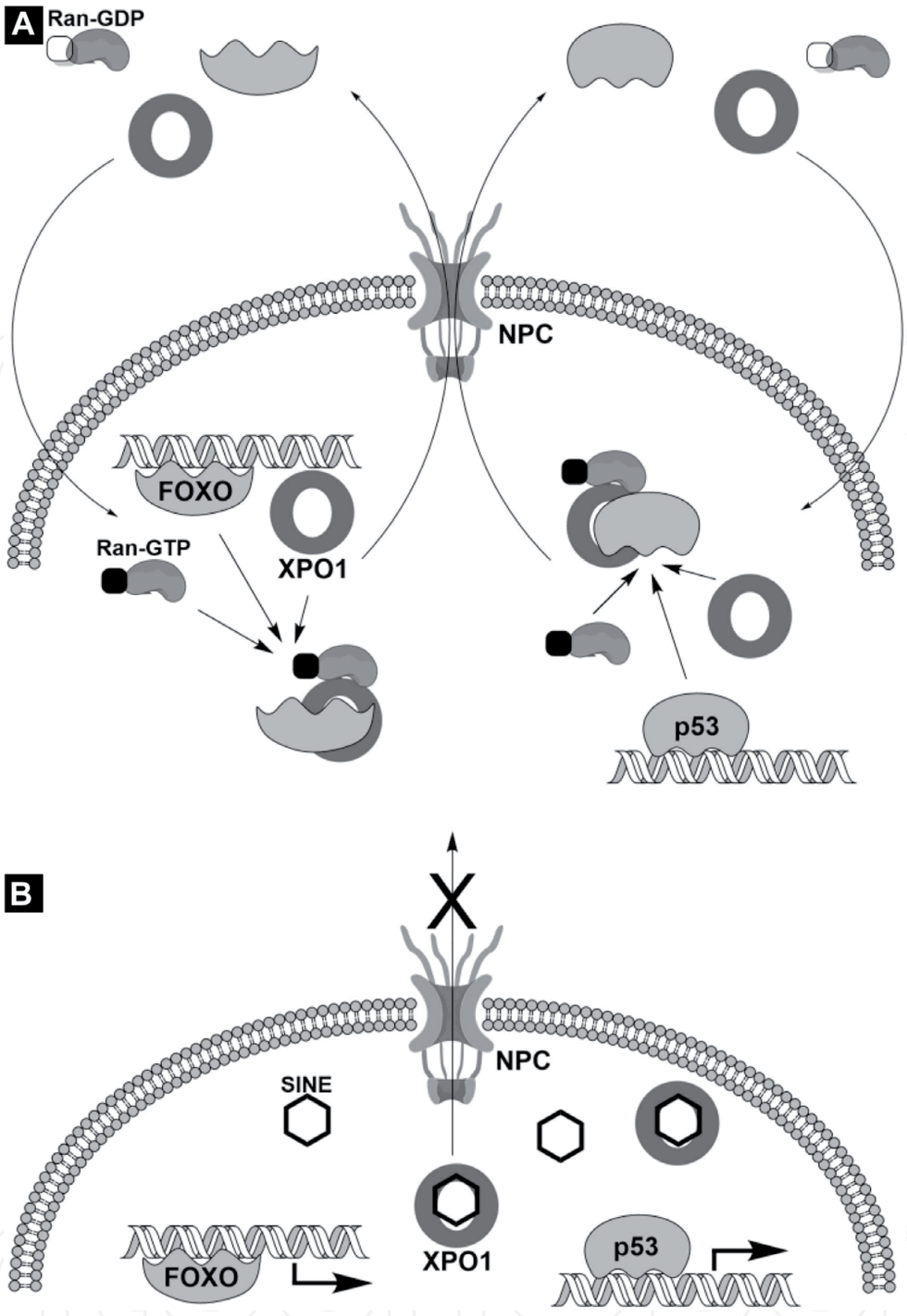

Figure 1.
Exportin 1-mediated nuclear export in multiple myeloma; Abbreviations: Ran-GDP and Ran-GTP – GDP or GTP bound Ras related factor; NPC – nuclear pore complex; SINE - selective inhibitor of nuclear export; FOXO – a subgroup of the Forkhead family of transcription factors, p53 – a tumor suppressor protein and transcription factor; XPO1 – exportin 1, also known as chromosomal maintenance 1 (CRM1); (A) XPO1 transports nuclear proteins out of the nucleus. Cargo proteins such as FOXO or p53 that are marked for export from the nucleus bind a pocket in XPO1 in the presence of the activated small G-protein, Ran. The active Ran-GTP-XPO1-cargo complex is exported from the nucleus through the nuclear pore complex driven by the concentration gradient of Ran-GTP across the nuclear membrane. Once in the cytoplasm, Ran-GTP is hydrolyzed to Ran-GDP, and the XPO1-cargo complex dissociates. (B) SINE compounds (Hexagons) bind to XPO1-Cys^{528} and occupy the cargo-binding pocket of XPO1 and prevent formation of the Ran-GTP-XPO1-cargo complex. The result is increased nuclear localization of tumor suppressor cargo proteins and upregulation of their transcriptional activity [15].

binding to cysteine 528 (Cys528) in the cargo proteins NES-binding pocket of exportin1 and contribute to cancer cell death [15]. All these drugs have been developed by Karyopharm Therapeutics Inc., Natick, MA.

2. Selinexor-a small molecule exportin 1 inhibitor

The structural formula of selinexor is shown in **Figure 2**. Selinexor is a first member of small molecule oral inhibitors of exportin 1 developed for the treatment of cancer. Selinexor in combination with a synthetic glucocorticoid dexamethasone was approved by the FDA (U.S. Food and Drug Administration) on July 3, 2019 for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies. Selinexor synergizes with dexamethasone and inhibits the mTOR pathway and subsequently induces cell death in multiple myeloma cells [19]. Selinexor increases the expression of glucocorticoid receptor and in combination with dexamethasone stimulates transcriptional activity of the glucocoticoid receptor [19]. Selinexor is studied in clinical trials also in many hematological and solid cancers [20–24]. The treatment with selinexor in preclinical and clinical studies resulted in nuclear localization of tumor suppressor proteins (eg p53 and FOXO3A), induced apoptosis and decreased proliferation. Selinexor reduces the expression of DNA damage repair proteins and sensitizes cancer cells to DNA damaging agents [25]. Selinexor blocks the transcription factor NF-κB and induces ribosomal stressby disruption of ribosomal subunits assembly [26].

Selinexor is orally bioavailable with a mean half-life 6–8 h after a single dose. Selinexor pharmacokinetics are not significantly affected by age, sex, ethnicity, renal impairment or mild hepatic impairment. Most frequent adverse events associated with selinexor treatment are thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhoea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnoea, and upper respiratory tract infection.

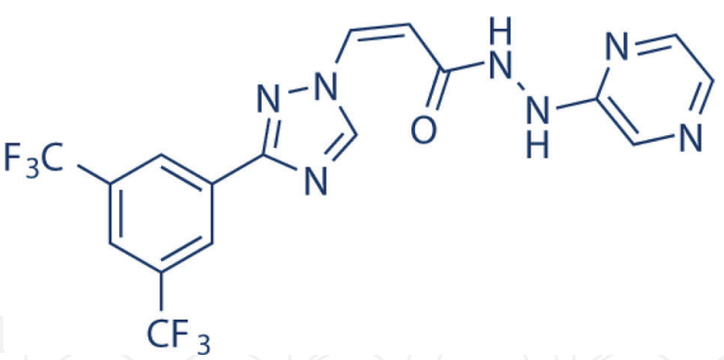

Figure 2.
Chemical structure of selinexor (alternative names: ATG-010, KPT-330, ONO7705, XPOVIO, CRM1 nuclear export inhibitor). Chemical name: (Z)-3-(3-(3,5-bis(trifluoromethyl)phenyl-1H-1,2,4-triazol-1-yl)-N´-(pyrazin-2-yl)acrylohydrazide.

3. The phase II STORM trial with selinexor plus low-dose dexamethasone in patients with multiple myeloma pretreated with bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, and an alkylating agent

Selinexor demonstrated small single-agent activity with an overall response rate achieved in 4% (2/57 heavily pre-treated patients with RRMM (about six prior therapies)) [27]. The response was considerably increased from 4 to 50% (6/12) when selinexor was combined with dexamethasone in a phase I trial in patients with advanced hematological malignancies (NCT 01607892) [27]. The phase II STORM trial (NCT02336815) with selinexor and dexamethasone combination in heavily pre-treated patients with RRMM had relatively quick responses. The primary

endpoint was overall response. Patients were given twice weekly oral doses of selinexor (80 mg) and dexamethasone (20 mg) in 28-day cycles [28, 29]. An overall response was recorded in 21% patients (16/78) or 26% (32/122) and median duration of response was 5 months. Patients required a lot of supportive care to mange many side effects. The most common adverse event was thrombocytopenia.

4. A multicenter, open-label, phase 1b/2, dose escalation trial STOMP in patients with relapsed or refractory multiple myeloma with a median of three prior therapies

The STOMP trial (NCT02343042) is a five arms study of selinexor, dexamethasone and either lenalidomide, pomalidomide, bortezomib, carfilzomib or daratumumab for the treatment of relapsed or refractory multiple myeloma with median of three prior therapies in order to evaluate the safety, tolerability and efficacy of these combinations, determining the maximum tolerated dose, the recommended phase 2 dose, overall response rate (ORR), and progression-free survival (PFS) [23, 24, 26]. Individual arms were described in abstracts No. 726, 1366, and 1393 on ASH 2020 meeting.

5. The randomized open-label, phase III international BOSTON trial in patients with relapsed or refractory multiple myeloma with a median of two prior therapies

The combination of selinexor and bortezomib once per week plus dexamethasone twice per week (SVd) was compared with bortezomib twice per week in combination with dexamethasone four times per week for the first six months and one half of this dose thereafter (Vd) [30]. Median PFS was longer with selinexor treatment: 13.93 months versus 9.46 months in the Vd group. The improvements in survival and response rates with selinexor were associated with higher rates of adverse events [30].

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